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Review

Exposure to pesticides and childhood leukemia risk: A systematic review and meta-analysis☆

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ABSTRACT

Despite the abundance of epidemiological evidence concerning the association between pesticide exposure and adverse health outcomes including acute childhood leukemia (AL), evidence remains inconclusive, and is inherently limited by heterogeneous exposure assessment and multiple statistical testing. We performed a literature search of peer-reviewed studies, published until January 2021, without language restrictions. Summary odds ratios (OR) and 95% confidence intervals (CI) were derived from stratified random-effects meta-analyses by type of exposure and outcome, exposed populations and window of exposure to address the large heterogeneity of existing literature. Heterogeneity and small-study effects were also assessed. We identified 55 eligible studies (n = 48 case-control and n = 7 cohorts) from over 30 countries assessing >200 different exposures of pesticides (n = 160,924 participants). The summary OR for maternal environmental exposure to pesticides (broad term) during pregnancy and AL was 1.88 (95%CI: 1.15–3.08), reaching 2.51 for acute lymphoblastic leukemia (ALL; 95%CI: 1.39–4.55). Analysis by pesticide subtype yielded an increased risk for maternal herbicide (OR: 1.41, 95%CI: 1.00–1.99) and insecticide (OR: 1.60, 95%CI: 1.11–2.29) exposure during pregnancy and AL without heterogeneity (p = 0.12–0.34). Meta-analyses of infant leukemia were only feasible for maternal exposure to pesticides during pregnancy. Higher magnitude risks were observed for maternal pesticide exposure and infant ALL (OR: 2.18, 95%CI: 1.44–3.29), and the highest for infant acute myeloid leukemia (OR: 3.42, 95%CI: 1.98–5.91). Overall, the associations were stronger for maternal exposure during pregnancy compared to childhood exposure. For occupational or mixed exposures, parental, and specifically paternal, pesticide exposure was significantly associated with increased risk of AL ($OR_{parental}$: 1.75, 95%CI: 1.08–2.85; $OR_{paternal}$: 1.20, 95%CI: 1.07–1.35). The epidemiological evidence, supported by mechanistic studies, suggests that pesticide exposure, mainly during pregnancy, increases the risk of childhood leukemia, particularly among infants. Sufficiently powered studies using repeated biomarker analyses are needed to confirm whether there is public health merit in reducing prenatal pesticide exposure.

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1. Introduction

Acute leukemia (AL) is the most common type of childhood cancer (0–14 years) accounting for up to 40% of pediatric cancer cases (Noone et al., 2017). Though the disease is rare at population level with an annual incidence of approximately 39 cases per million children, a small, but steady increase in the incidence of AL has been reported over the past three decades (Noone et al., 1975–2015). Despite striking advances in disease survival, childhood AL remains the second leading cause of death worldwide following physical injury; childhood AL deaths are responsible for around 131,000 years of life lost (YLL) in the USA (Collaborators, 2019). Long-term AL survivors are likely to experience severe adverse health outcomes throughout their adulthood (Erdmann et al., 2019; Landier et al., 2015). In particular, it is estimated that 40% of adults older than 35 years who have been diagnosed with pediatric cancer will experience life-threatening complications with mortality rates up to five times higher compared to their healthy counterparts (Armenian and Robison, 2013). Thus, primary prevention of this disease remains an utmost priority (Metayer et al., 2016).

Extensive research has focused on the multifactorial etiology of childhood AL involving an intricate interaction between a strong genetic component and many lifestyle influences (Buffler et al., 2005; Wiemels, 2012). The increasing incidence of the disease could be attributed, among others, to environmental determinants. Emerging evidence suggests that environmental contaminants may also play a crucial role. Pesticides represent an increasingly widespread environmental exposure and some specific compounds have the potential to accumulate in human tissues. This is a concern especially in children whose enzymatic and metabolic systems limits their ability to detoxify and excrete pesticides; in addition to this, the greater cellular division in children renders them more vulnerable to hazardous complications including acute toxic effects on their respiratory, gastrointestinal, nervous, and endocrine systems (Sheets, 2000; Infante-Rivard and Weichenthal, 2007). In recent years, there have been growing concerns about possible adverse health effects of low-level pesticide exposure during pregnancy or childhood generating a substantial number of epidemiologic studies (Panel on Plant Prote, 2017). Several of these studies have examined the association between environmental or occupational pesticide exposure and risk of childhood cancer, specifically focusing on leukemia (Infante-Rivard and Weichenthal, 2007; Bailey et al., 2014; Bailey et al., 2015; Patel et al., 2020a; Zahm, 1999; Meinert et al., 2000). Various systematic reviews and meta-analyses have also studied the association between environmental or occupational pesticide exposure and childhood AL risk (Turner et al., 2010; Van Maele-Fabry et al., 2019; Van Maele-Fabry et al., 2010; Van Maele-Fabry et al., 2011; Chen et al., 2015; Wigle et al., 2009). Overall, to-date evidence remains inconclusive and is inherently limited by heterogeneous exposure and outcome assessment (type of pesticides, exposed individual, window of exposure, type of leukemia), which, by necessity, result in multiple statistical testing that increase the probability of chance findings (Turner et al., 2010; Van Maele-Fabry et al., 2019; Metayer and Buffler, 2008).

Acknowledging these inherent limitations, in the present study, we aimed to comprehensively and systematically appraise the currently available epidemiological evidence on the association of exposure to pesticides with different types of childhood AL, including acute lymphoblastic (ALL), acute myeloid (AML) and infant leukemia, with a special focus on the methodological issues of literature.

2. Methods

2.1. Data sources and search

The present systematic review and meta-analysis adheres to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary Table 1) (Welch et al., 2016).

We searched for peer-reviewed original epidemiological research pertaining to pesticide exposure and risk of childhood AL. Our previous systematic literature search was conducted between January 1, 2006 and July 5, 2019 for the European Food and Safety Authority (EFSA). In the present systematic review and meta-analysis, we updated the literature search without publication date restriction using the same search strategy and inclusion criteria. Two reviewers independently searched the MEDLINE and EMBASE databases; potential discrepancies were resolved by consensus. Screening was initially performed through a titles-first approach, followed by title and abstract screening (Mateen et al., 2013). Reference lists of all articles meeting the inclusion criteria and of relevant review articles were examined to identify studies that may have been missed by the initial database search.

The literature search was limited to studies on humans, and no language or other search restriction criteria were applied. For maximum sensitivity, we did not include any outcome-related search terms in the algorithm. The search algorithm focused on pesticide-related terms, identified through the MEDLINE MESH terms and EMBASE classification trees on pesticides. The following algorithm was thus developed: (pesticid OR 'pesticide'/exp OR 'chemical pest control'/exp OR fungicid OR 'fungicide'/exp OR herbicid OR 'herbicide'/exp OR insecticid OR 'insecticide'/exp OR molluscacid OR 'molluscacide'/exp OR molluscicid OR 'molluscicide'/exp OR rodenticid OR 'rodenticide'/exp OR carbamat OR 'carbamate'/exp OR pyrethroid* OR 'pyrethroid'/exp OR 'chlorinated hydrocarbon'/exp OR 'agricultural chemical'/exp) NOT warfarin AND [humans]/lim. Last literature search was performed on January 7, 2021.

2.2. Study selection

Eligible publications were cohort, case-control and cross-sectional studies that examined maternal, paternal or parental exposure to pesticides during specific windows of exposure (preconception, pregnancy or childhood) in relation to any type of childhood (0–14 years) AL. We searched for environmental (residential or household), occupational or joint exposures to any unspecified pesticide and pesticide subgroups (insecticides, herbicides, fungicides). The exposure assessment also covered biomarkers of pesticide exposure, self-reported frequency of pesticide use or other records documenting use or contact with these substances, if such an information was available. Reviews, case reports/series and ecologic studies were excluded. In addition, we excluded studies or analyses examining environmental toxicants not strictly classified as pesticides, namely arsenic, a-, b-hexachlorocyclohexane (HCH), lead, dioxins (and dioxin-like compounds), polychlorinated biphenyls (PCBs), and polychlorinated dibenzofurans (PCDFs). If a study evaluated a pesticide, but also some other toxicants not strictly classified as pesticides, we included only the analysis of the pesticide. Lastly, studies on acute pesticide poisoning and Agent Orange studies on very high exposure doses were also excluded.

All eligible studies were assessed for overlap, based on geographic location, data sources, diagnostic period, age range and number of cases. Particularly, the case-control studies participating in the multicenter Childhood Leukemia International Consortium (CLIC) pooled analysis (Metayer et al., 2013a), as well as the cohort studies participating in the multicenter International Childhood Cancer Cohort Consortium (I4C) (Tikellis et al., 2018) were evaluated for overlapping populations with the remaining eligible studies. Whenever two or more articles studied the same population, the same pesticides and the same exposure period (complete overlap), the largest or most recent publication was included in the analysis.

2.3. Data extraction and quality assessment

Pairs of investigators independently performed the data extraction for each eligible study. Information was extracted on the name of first author; the journal and publication year; the study design; the type and name of pesticide(s) assessed; how exposure was assessed

(questionnaire/biomarker); the person (mother/father/both parents/child) on which the exposure assessment was measured; the window of exposure (preconception/pregnancy/childhood); the outcome definition as reported in the study; the effect estimate and its uncertainty; the comparison level; origin of the population; total sample size and number of cases and controls.

The data extraction database included study quality indicators, in particular, elements from the validated Item Bank for Assessment of Risk of Bias and Precision for Observational Studies of Interventions or Exposures (RTI item bank, 2012) to evaluate the risk of bias and precision of the eligible studies included in the present systematic review (Viswanathan and Berkman, 2012).

2.4. Data synthesis and analysis

The statistical analyses were stratified by the type of exposure (environmental, occupational or both), the exposed individual (mother/father/both parents/child), window of exposure (at any time, preconception, pregnancy and childhood) and type of leukemia (overall AL, ALL and AML). The main analyses focused on the association of childhood AL with exposure to unspecified pesticides, pesticide subgroups (herbicides, insecticides, fungicides, rodenticides) and any specific classes or biomarkers.

We performed meta-analyses where data were available in more than two studies. When multiple exposure definitions on the same type of pesticides were presented in a study, the most inclusive definition of pesticide exposure was included in the analysis. Random-effects meta-analyses were used to combine the association estimates of eligible studies with the DerSimonian-Laird estimator for the between-study variance ($\tau 2$) and summary OR with corresponding 95% CI were calculated. We used the Cochran's Q statistic to assess between-study heterogeneity and I (Noone et al., 1975–2015) (ranging from 0% to 100%) as the percentage of total variation in effect estimates that is due to heterogeneity rather than sampling error (DerSimonian and Laird, 1986) (Ioannidis, 2008; Ioannidis et al., 2007; Higgins and Thompson, 2002; Higgins et al., 2003). Different exposure estimates were often used across the studies, such as binary categories ("any" versus "never" exposed or "high" versus "low" exposed), tertiles, quartiles or quintiles, whereas only a few studies evaluated the linear exposure to pesticides. Opting for comprehensiveness, we followed a categorical analytical approach using the "any versus never" exposure to pesticides. To enable a consistent and comparable approach, estimates on other than binary exposure contrasts (i.e. tertiles, quartiles, quintiles) were harmonized and adjusted to the desired binary categories using the method

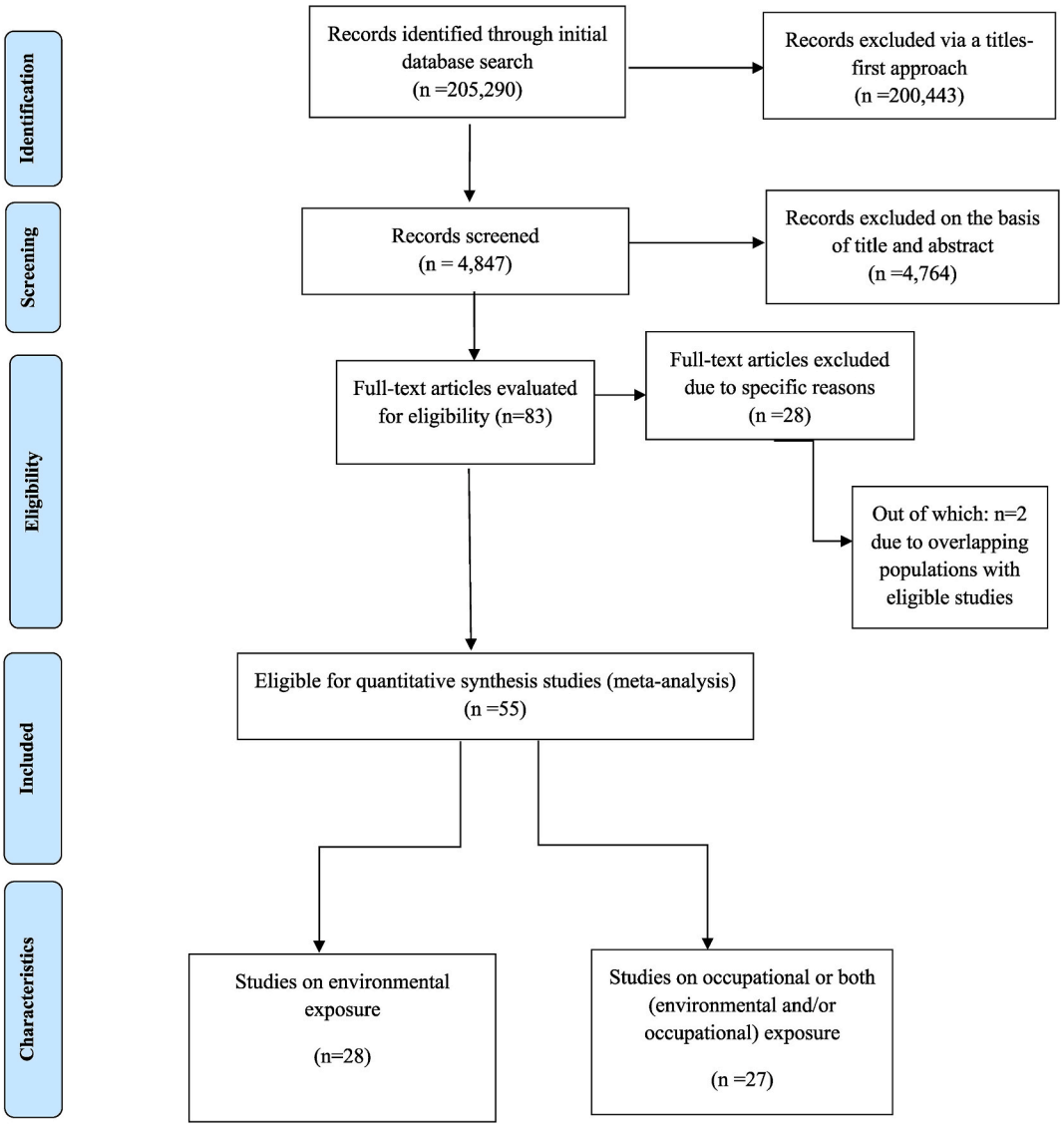

Fig. 1. Flow chart of the study selection process.

described by Hamling et al. (2008).

Sensitivity analyses per AL subtype (infant AL, ALL and AML) were also performed. We assessed small study effects (an indication of publication bias) by visual inspection of funnel plots and by the Egger's test in meta-analyses including at least 5 studies (Egger et al., 1997).

All analyses were performed using the STATA Software (v13.0, Stata Corporation, College Station, TX, USA) and p-values ≤ 0.05 were deemed significant.

3. Results

3.1. Study characteristics and quality evaluation

The initial literature search in MEDLINE and EMBASE databases retrieved 205,290 articles, of which 83 were evaluated for eligibility following the titles-first and title-and-abstract approaches as shown in the flow chart of the study selection process (Fig. 1). Twenty-seven publications (Noone et al., 1975–2015; Zahm, 1999; Alderton et al., 2006; Canalle et al., 2004; Flower et al., 2004; Kaatsch et al., 1996; Kishi et al., 1993; Kristensen et al., 1996; Maskarinec, 2005; Monge et al., 2004; Mulder et al., 1993; Mulder et al., 1994; Reynolds et al., 2005a; Reynolds et al., 2002; Safi, 2002; Schreinemachers et al., 1999; Schwartzbaum et al., 1991; Soldin et al., 2009; Thorpe and Shirmohammadi, 2005; Urayama et al., 2007; Valcke et al., 2005; Wu et al., 2003; Keegan et al., 2012; McKinney et al., 2003; Miligi et al., 2013; Bertazzi et al., 1999; Kaatsch et al., 1998; Ohlander et al., 2020) and a conference abstract were excluded due to specific reasons (Supplementary Table 2). Among these studies, two were excluded due to duplicate data from the Northern California Childhood Leukemia Study (NCCLS) (Urayama et al., 2007) and a German case-control study (Kaatsch et al., 1998). Thus, 55 studies were deemed eligible, of which 28 publications assessed environmental and 27 occupational or joint (occupational and environmental) exposures to pesticides in relation to childhood AL.

Descriptive characteristics of the eligible studies are summarized in Supplementary table 3. The majority of studies (n = 48; 87.3%) were of case-control design[12-14, 17, 63-106] yielding a total sample size of 169,227 participants (34,477 cases/134,750 controls). In addition, there was also data from seven cohort studies (1502 total incident cases/8,656,628 total cohort size) (Patel et al., 2020a; Cha et al., 2014; Fear et al., 1998; Feychting et al., 2001; Rodvall et al., 2003; Coste et al., 2020; Patel et al., 2020b). Of the 55 eligible studies, 22 were based in America (15 in North America and 7 in South America), 18 in Europe, 10 in Asia and 1 in Antarctica region. In addition, four multicenter studies (two CLIC (Bailey et al., 2014; Bailey et al., 2015), one I4C (Patel et al., 2020a), and one multicenter study from Europe, South America, Africa and Asia (Alexander et al., 2001)) were retrieved.

Overall, more than 200 different exposures of pesticides were studied. The prevalence of exposure varied widely among the eligible studies ranging approximately between 2% and 15%; higher prevalence rates were noted in studies assessing occupational exposures to pesticides (range: 33–48%; Supplementary table 3). Though the overwhelming majority of studies (n = 48) assessed exposure to pesticides (broad term) or pesticide subgroups (insecticides, herbicides, fungicides), some studies also attempted to collect information on specific classes of pesticides or specific compounds. In addition, two studies assessed biomarkers in urine or bone marrow reflecting internal exposure to specific substances (Zhang et al., 2015; Rau et al., 2012), while two others quantified biomarker levels by using dust samples reflecting external exposure (Metayer et al., 2013b; Ward et al., 2009). There were few data regarding frequency or duration of pesticide exposure, with most studies reporting only "any versus never" use of the pesticide of interest. Many studies assessed pesticide exposure separately for different windows of exposure: preconception, pregnancy and childhood, whereas the majority of analyses were adjusted for at least a range of sociodemographic and maternal characteristics. Overall, based on the RTI item bank, high quality was recorded in three eligible studies, whereas the remaining publications were assigned an intermediate quality rating (Supplementary Table 3). The quality of studies was mainly compromised by the partially robust assessment of exposure based on residential history, occupational history and self-administered or interview-based questionnaires, as well as the partially specific measurement of exposure based on broad categories of pesticides.

3.2. Pesticide exposure at any time

Twenty-one studies assessed the exposure to pesticides at any time during preconception, pregnancy or childhood in relation to childhood AL risk. The majority of these studies (n = 16; 76%) examined occupational or both occupational and environmental exposures to pesticides. Most studies assessed broad categories of pesticides, whereas two studies measured biomarkers of organochlorines (OC) and organophosphate (OP) pesticides in dust and urine samples, respectively (Ward et al., 2009; Zhang et al., 2015). In total, 156 different analyses were undertaken yielding 44 statistically significant associations, mainly concerning any pesticide or broad categories of pesticides (herbicides, insecticides, fungicides, rodenticides) in relation to childhood AL.

For environmental exposure to pesticides and AL risk, the meta-analyses showed mostly non-statistically significant associations (Supplementary Table 4), except for the associations between maternal (sOR: 1.94, 95% CI: 1.03–3.64; n = 2 studies; I (Noone et al., 1975–2015) = 88%) and parental (sOR: 2.25, 95% CI: 1.39–3.62; n = 2 studies; I (Noone et al., 1975–2015): 0%) environmental exposure to any pesticide and childhood AL risk. For occupational or mixed exposures, parental exposure to any unspecified pesticide was significantly associated with 1.8-fold higher risk of childhood AL (sOR: 1.75, 95% CI: 1.08–2.85; n = 6 studies; Fig. 2a). Statistically significant between-study heterogeneity (I (Noone et al., 1975–2015): 78%, $p < 0.0001$) was observed, but no prominent small-study effects bias (Egger's test $p = 0.50$; Supplementary Figure 1). Of note is that the significant association of occupational exposure to pesticides with AL risk was mainly confined to paternal occupational exposure (sOR: 1.20, 95% CI: 1.07–1.35; n = 5 studies; Fig. 2b) without significant heterogeneity (I (Noone et al., 1975–2015): 6%, $p = 0.37$; Supplementary Table 4) rather than maternal exposure (Fig. 2c).

3.3. Pesticide exposure during preconception

Seventeen studies examined preconception as the time window of exposure. Of the 112 discrete analyses, 40 were statistically significant stemming from nine reports (Bailey et al., 2014; Bailey et al., 2015; Ferreira et al., 2013; Infante-Rivard and Sinnett, 1999; Monge et al., 2007; Petridou, 2001; Rudant et al., 2007; Ma et al., 2002; Hernandez-Morales et al., 2009b). One of these studies reported a statistically significant association between paternal occupational exposure to OP pesticides and childhood AL (OR: 1.50, 95% CI: 1.00–2.20) (Monge et al., 2007). The remaining eight studies assessed broader categories of pesticides and showed significant associations between occupational or environmental exposure to any pesticide or pesticide subgroups before pregnancy and childhood AL; yet, the results were of weak to modest effect. Both CLIC studies reported significant associations between unspecified pesticide exposure before pregnancy and childhood AL risk. In particular, the first CLIC study showed a significantly higher risk for childhood ALL among children whose parents reported environmental exposure to insecticides/miticides (OR: 1.34, 95% CI: 1.19–1.51), herbicides (OR: 1.23, 95% CI: 1.04–1.45) and rodenticides (OR: 1.39, 95% CI: 1.10–1.76) 1–3 months before pregnancy (Bailey et al., 2015). In the second CLIC study, a statistically significant association was also found between paternal occupational exposure around conception and childhood ALL, and especially B-cell ALL (OR: 1.19, 95% CI: 1.03–1.37) based on 8169 cases and 14,201 controls (Bailey et al., 2014).

Our quantitative synthesis showed a summary OR for maternal

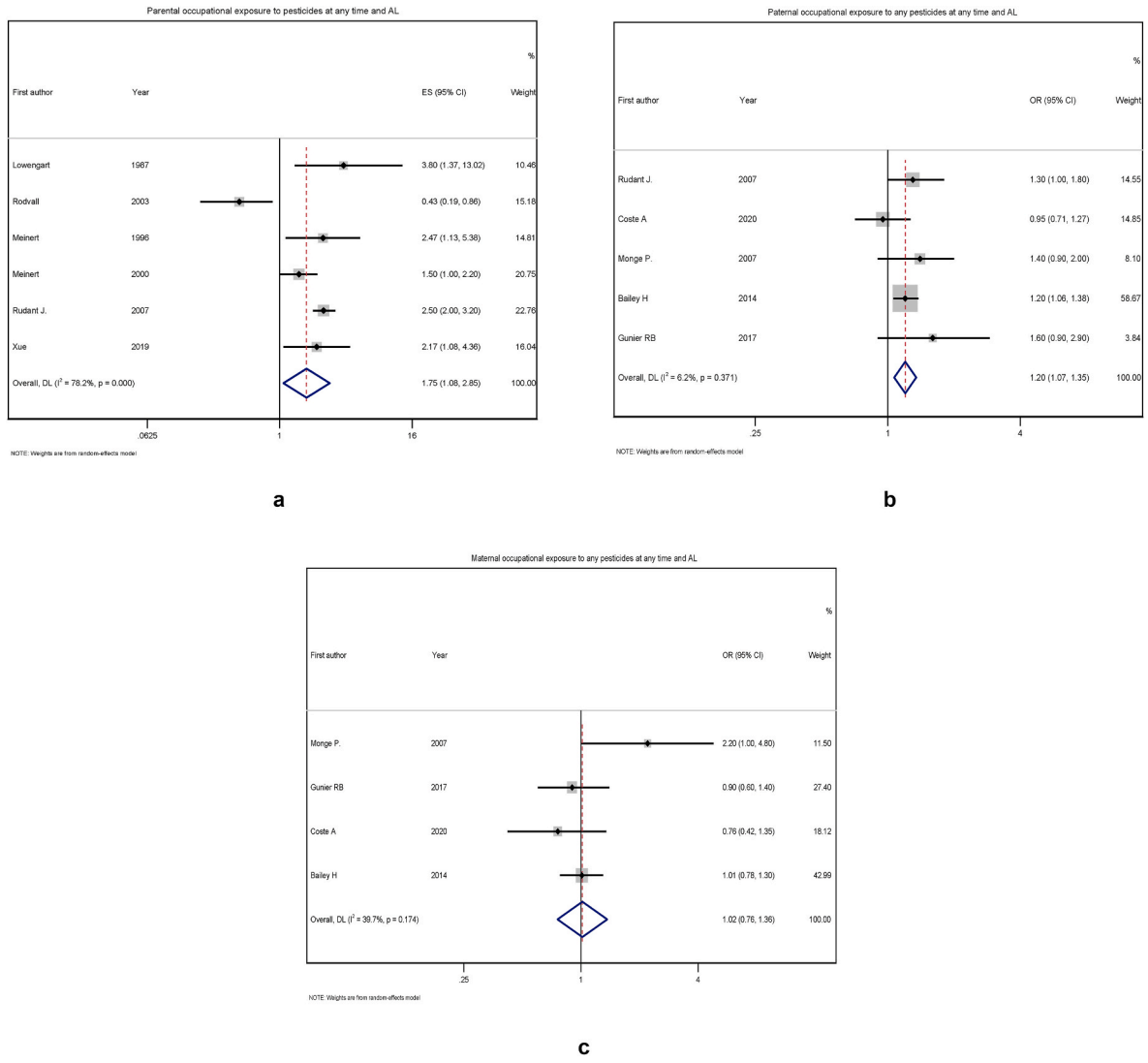

Fig. 2. Forest plot for the association between (a) parental, (b) paternal and (c) maternal occupational exposure to pesticides at any time during preconception, pregnancy or childhood and risk of childhood acute leukemia.

environmental exposure to pesticides during preconception and AL of 1.98 (95% CI: 1.46–2.70; n = 2 studies) without heterogeneity (I (Noone et al., 1975–2015): 0.0%, $p = 0.33$; Supplementary Table 4). The association was stronger for maternal occupational or mixed exposure and ALL risk (sOR: 2.52, 95% CI: 1.38–4.59). Non-significant associations were observed for specific pesticide subgroups (herbicides, insecticides or rodenticides) and AL risk during the preconception exposure window (Supplementary Table 4).

3.4. Pesticide exposure during pregnancy

Twenty-eight studies provided information on pesticide exposures during pregnancy. Around half of these studies (n = 15) examined environmental exposure, which was assessed through self-administered or interview-based questionnaires. The remaining studies examined occupational or mixed exposure to pesticides assessed through job exposure matrix (JEM) or occupational history. None of the 28 studies measured biomarkers of pesticide exposure in biological samples. The majority of studies (n = 20) focused on maternal exposure to pesticides, nine on paternal and seven on parental pesticide exposure. Overall, 367 separate analyses were performed, of which 28% of the results (n = 103) were statistically significant. In particular, the first multicenter study from CLIC reported a statistically significant association between childhood AML and maternal occupational exposure to pesticides during pregnancy assessed through JEM (OR: 1.94, 95% CI: 1.19–3.18) (Bailey et al., 2014). The second CLIC study also showed a significantly increased risk for ALL among children whose parents reported household exposure to pesticides (OR: 1.43, 95% CI: 1.32–1.54), and especially insecticides/miticides (OR: 1.28, 95% CI: 1.18–1.38) and herbicides (OR: 1.34, 95% CI: 1.19–1.50) during the index pregnancy (Bailey et al., 2015). In addition, a study from Costa Rica showed a borderline significant association between paternal occupational exposure to benzimidazoles and overall AL (OR: 2.20, 95% CI: 1.00–5.20) (Monge et al., 2007). The vast majority of statistically significant results (n = 56 out of 76) were reported from three studies only, the French ESCALE case-control study (Rudant et al., 2007), the Multi-institutional Brazilian Study of Infant Leukemia (Ferreira et al., 2013) and the one CLIC multicenter study (Bailey et al., 2015). In particular, in the ESCALE study insecticide use during pregnancy was significantly associated with childhood AL (OR: 2.10, 95% CI: 1.70–2.50), whereas paternal household use of pesticides was also related to AL (OR: 1.50, 95% CI: 1.20–1.80) in this study. On the other hand, the recent multicenter study from I4C showed non-significant associations between paternal occupational exposure to any pesticide or pesticide subgroups during

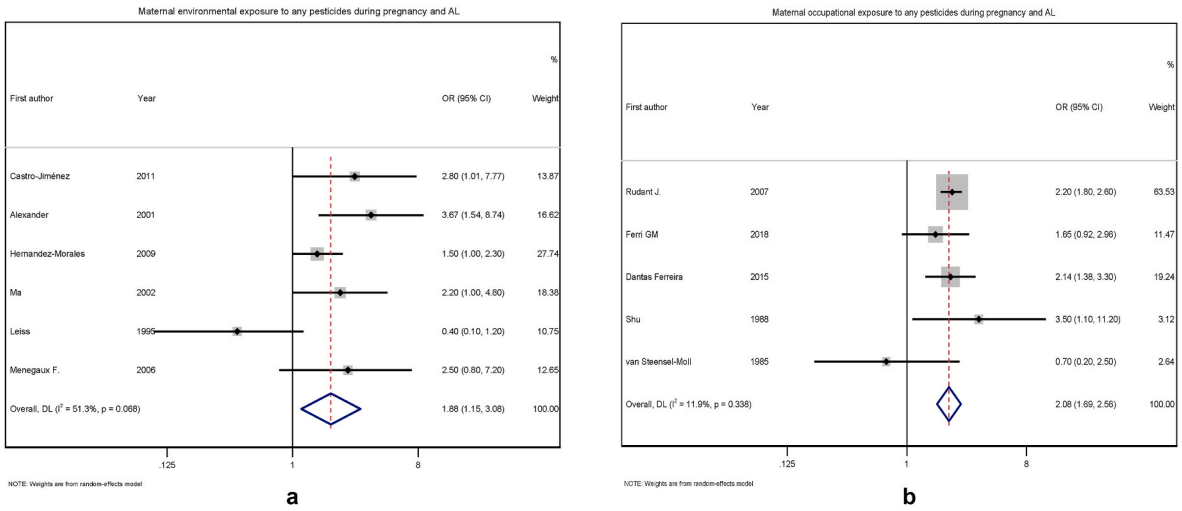

Fig. 3. Forest plot for the association between (a) maternal environmental and (b) maternal occupational exposure to pesticides during pregnancy and risk of childhood acute leukemia.

pregnancy and childhood AL risk (Patel et al., 2020a). Of note is the borderline significant association of herbicides (HR: 3.22, 95% CI: 0.97–10.68) and insecticides (HR: 2.86, 95% CI: 0.99–8.23) with AML risk in this study.

The quantitative synthesis showed a statistically significant association of maternal environmental exposure to pesticides with AL (sOR: 1.88, 95% CI: 1.15–3.08; n = 6 studies; I (Noone et al., 1975–2015) = 51.3%; Fig. 3a), especially ALL risk (sOR: 2.51, 95% CI: 1.39–4.55; n = 3 studies; I (Noone et al., 1975–2015) = 0.0%; Supplementary Table 4). No prominent small-study effect was observed (Egger's test $p = 0.81$; Supplementary Figure 2). The meta-analysis further showed statistically significant associations of herbicide (sOR: 1.41, 95% CI: 1.00–1.99) and insecticide (sOR: 1.60, 95% CI: 1.11–2.29) exposure with AL risk without significant between-study heterogeneity ($p = 0.12$–0.34). Among occupational exposures, maternal exposure to pesticides (sOR: 2.08, 95% CI: 1.69–2.56; Fig. 3b), and especially insecticides (sOR: 2.08, 95% CI: 1.73–2.49), during pregnancy was also associated with significantly higher risk of childhood AL. Meta-analyses restricted to infant AL, ALL and AML were only feasible for maternal exposure to pesticides during pregnancy. Of note is the high magnitude risk observed for infant ALL (sOR: 2.18, 95% CI: 1.44–3.29) and the even highest for infant AML (sOR: 3.42, 95% CI: 1.98–5.91) in relation to maternal pesticide exposure during pregnancy (Supplementary Table 5), without between-study heterogeneity ($p = 0.27$–0.81).

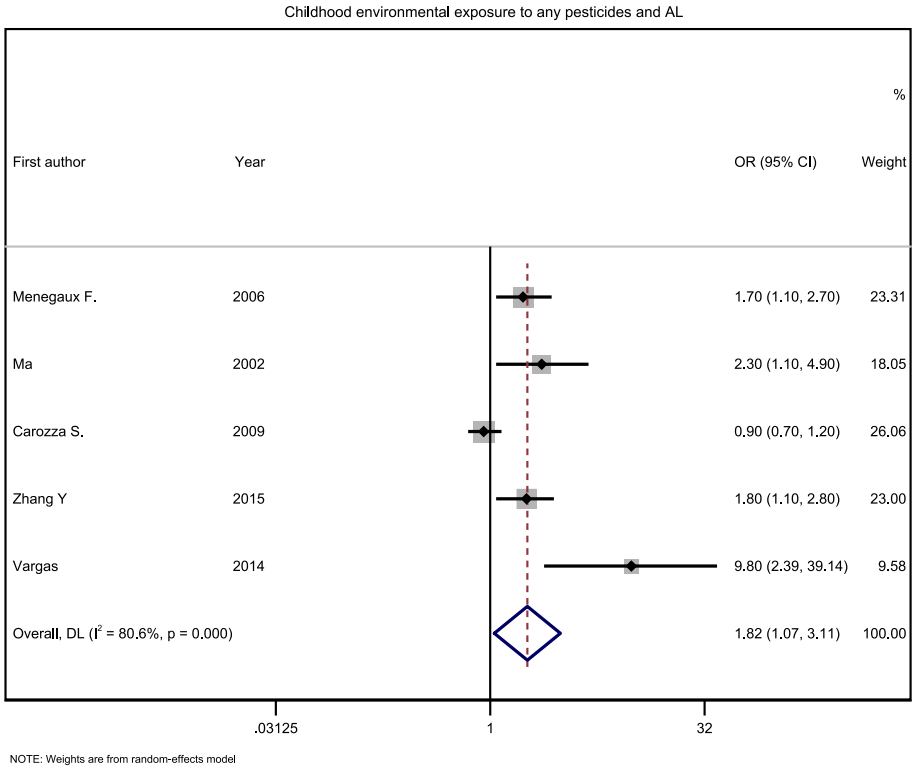

Fig. 4. Forest plot for the association between exposure to pesticides during childhood and risk of childhood acute leukemia.

3.5. Pesticide exposure during childhood

Twenty-nine studies with information on pesticide exposure during childhood were identified. Five studies examined exposure to pesticides during infancy (Ferreira et al., 2013; Monge et al., 2007; Bailey et al., 2011; Ma et al., 2002; Rull et al., 2009b), whereas the remaining studies assessed exposure across variable periods during childhood. The majority of identified studies (n = 15) examined exposure of children to pesticides, whereas the remaining studies assessed maternal, paternal or parental pesticide exposure during childhood in relation to the development of AL in the index child. Seventeen studies concentrated on environmental exposure to pesticides, whereas one study examined endosulfan, which is no longer in use (Rau et al., 2012). Of the 188 different analyses performed, 59 results were statistically significant concerning herbicides, insecticides and fungicides in relation to childhood AL; yet, the magnitude of the effect ranged between 1.00 and 1.60 in the majority of statistically significant associations (data not shown in Tables).

The summary OR between childhood exposure to any pesticides and AL risk was 1.82 (95% CI: 1.07–3.11) based on five studies (Fig. 4). Of note is the significant association of insecticide exposure with ALL (sOR: 1.48, 95% CI: 1.17–1.86; n = 2 studies) without significant between-study heterogeneity (p = 0.57; Supplementary Table 4). Overall, the meta-analysis provided some evidence for an association between childhood exposure to pesticides and AL, but this was in general weaker than the exposure during pregnancy.

3.6. Compound-specific pesticide exposures

Seven studies, 4 based in the USA (Metayer et al., 2013b; Ward et al., 2009; Reynolds et al., 2005b; Park et al., 2020), 1 in Denmark (Patel et al., 2020b), 1 in Costa Rica (Monge et al., 2007) and 1 in Brazil (Ferreira et al., 2013) examined compound-specific pesticide exposures in relation to childhood AL yielding 222 different associations (Supplementary Table 6). Only 37 of the 222 associations were statistically significant stemming from four studies (Ferreira et al., 2013; Reynolds et al., 2005b; Park et al., 2020; Patel et al., 2020b) and were confined mainly to maternal exposure during pregnancy. In particular, the Brazilian Multi-institutional Study of Infant Leukemia reported overall 23 associations for compound-specific exposures, and showed a significantly higher risk of childhood ALL related to maternal exposure during pregnancy to permethrin (OR: 2.47, 95% CI: 1.17–5.25), imiprothrin (OR: 2.61, 95% CI: 1.06–6.93) and esbiothrin (OR: 3.03, 95% CI: 1.13–8.09), all of them being type I pyrethroid insecticides (Ferreira et al., 2013). Likewise, statistically significant results were also reported for childhood AML in relation to maternal exposure during pregnancy to prallethin (OR: 8.06, 95% CI: 1.17–55.65), permethrin (OR: 7.28, 95% CI: 2.60–20.38), esbiothrin (OR: 3.71, 95% CI: 1.18–11.62), d-phenothrin (OR: 8.43, 95% CI: 1.59–44.75) and d-allethrin (OR: 6.19, 95% CI: 2.07–18.56) in the same study. By contrast, the association of maternal exposure to imiprothrin with AML showed a trend towards statistical significance (OR: 3.41, 95% CI: 0.98–11.9). These results were, in general, of large effect size, but merit cautious interpretation as they stem from a single study group without appropriate adjustment for multiple testing (Ferreira et al., 2013). In a USA case-control study by Reynolds et al. (1990–1997; N = 2189 cases and N = 4335 controls), maternal exposure during pregnancy to the dithiocarbamate, metam sodium (OR: 2.05, 95% CI: 1.01–4.17) and to the organochlorine miticide, dicofol (OR: 1.83, 95% CI: 1.05–3.22) were both associated with statistically significantly higher risk of childhood AL (Reynolds et al., 2005b). A borderline significant association between childhood exposure to alachlor/chlorthal and ALL risk (OR: 2.56, 95% CI: 0.99–6.63) was reported in the second USA case-control study by Metayer et al. (2001–2007; N = 269 cases and N = 333 controls) (Metayer et al., 2013b). By contrast, non-statistically significant results were shown for paternal exposure to cooper and risk of childhood AL (Monge et al., 2007). A recent USA publication (Park et al., 2020) studied the association between environmental exposure to different classes of pesticides during pregnancy, assessed through residential history, and childhood AL risk reporting 160 different associations, of which 24 were statistically significant and mainly confined to ALL risk. Lastly, another recent study in Denmark (Patel et al., 2020b) assessed the association of maternal occupational exposure to specific pesticides during pregnancy with AL reporting 30 different associations. Three of the 30 associations were statistically significant yielding an increased risk, by 2.5–2.9 times, for AL in relation to the herbicides prosulfocarb (OR: 2.90, 95% CI: 1.30–6.10), thifensulfuron-methyl (OR: 2.70, 95% CI: 1.20–5.90) and bentazone (OR: 2.50, 95% CI: 1.10–5.30). Overall, the large heterogeneity in the type of exposure, exposure window, exposed subject (parents or child) and type of outcome resulted in a small number of identified studies per exposure (n = 1) which did not fulfill the criterion for quantitative synthesis of the compound-specific pesticide exposures.

4. Discussion

4.1. Principal findings

To our knowledge, this is the largest comprehensive systematic review and meta-analysis including all types of pesticide exposures and all types of childhood leukemia. Despite the large volume of available evidence stemming from 52 studies, a combined quantitative synthesis of all eligible studies was not feasible owing to the large variability in definitions of pesticide exposure, outcomes and windows of exposure (preconception, pregnancy or postnatal). Acknowledging this variability in study design, we followed a more stringent methodological approach based on stratified meta-analyses, which minimized the between-study heterogeneity in the majority of our analyses. Overall, the findings of our meta-analysis lend support to the hypothesis that environmental long-term exposure to pesticides increases the risk of childhood AL by approximately 1.5–2 times. Based on the evidence provided herein, the association was stronger for exposure during pregnancy compared to childhood exposure, and was, as expected, mainly confined to maternal rather than paternal exposure, as well as to infant than overall childhood leukemia. Among specific pesticide subtypes, insecticides and herbicides were both associated with significantly higher risk of childhood AL, and especially ALL. No prominent small study effect was found in most analyses.

4.2. Comparison with previous literature

The results of the present systematic review, including a larger number of identified publications up to 2020, are in general congruent with previous systematic reviews and meta-analyses. A direct comparison with these studies is not feasible due to different methodological approaches of reviewing published literature including different search strategy and eligibility criteria. Previous meta-analyses most frequently examined exposure to pesticides during pregnancy or childhood, and they focused either on environmental or on occupational exposure in relation to childhood AL (Bailey et al., 2014; Bailey et al., 2015; Turner et al., 2010; Van Maele-Fabry et al., 2019; Van Maele-Fabry et al., 2010; Van Maele-Fabry et al., 2011; Chen et al., 2015; Wigle et al., 2009). Consistently with our study, the most recent meta-analysis (n = 15 studies) reported a statistically significant association between environmental pesticide exposure and childhood AL (pooled OR: 1.57, 95% CI: 1.27–1.95) without evidence of publication bias; the highest risks were found for AML among children younger than 2 years (Van Maele-Fabry et al., 2019). Older meta-analyses including studies published up to 2009 also reported significant associations of environmental and especially indoor exposure to pesticides, insecticides and herbicides during pregnancy with childhood AL risk (Turner et al., 2010; Van Maele-Fabry et al., 2011).

4.3. Biological plausibility of associations

The majority of childhood leukemia cases (around 90%) have an unclear etiology (Wiemels, 2012; Greaves, 2006); however, it is widely recognized that this disease has a multifactorial causal mechanism and that the timing of environmental exposures and genetic changes must be considered (Buffler et al., 2005). Over the last decades, the occurrence of leukemia in children has shown a rise that can be partially attributed to the increased exposure to different chemical risk factors (e.g. occupational exposures, air pollution, pesticides, solvents, dietary factors etc.) (Wiemels, 2012). Consistently with previous research, the present study has shown a possible link between childhood leukemia and environmental or occupational exposure to pesticides during preconception, pregnancy or early childhood. Despite the sound epidemiological evidence linking pesticide exposure during the aforementioned different reproductive stages with childhood leukemia, robust underlying pathological mechanisms still remain unknown; in particular, the first initiating molecular event has not yet been identified (Panel on Plant Prote, 2017; Hernandez and Menendez, 2016).

Most of the available evidence does not make a distinction between infant and childhood leukemia. The present study considered them separately and found significant associations of both entities with pesticide exposure. Childhood leukemia is a biologically heterogeneous disease of immature hematopoietic progenitors that consists of multiple subtypes depending on the cell type and lineage involved (lymphoid or myeloid progenitors) (Panel on Plant Prote, 2017). By contrast, infant leukemia is a rarer disease that manifests soon after birth (in the first year of life) and originates from a single, severe hit to fetal hematopoietic stem and progenitor cells (HSPC) during a critical developmental window of vulnerability (Greaves, 2015; Sanjuan-Pla et al., 2015). Hence, infant leukemia is considered an intrauterine developmental disease involving more immature precursors and eliciting different features and pathogenesis than the more frequent childhood leukemia (Ross et al., 1996).

For infant leukemia, a number of chemicals, particularly bioflavonoids, chemotherapy agents (etoposide, doxorubicin and epirubicin) and the pesticide chlorpyrifos can target HSPCs in the fetal liver where they inhibit topoisomerase II, and subsequently can produce DNA double-strand breaks (Supplementary Figure 3) (Panel on Plant Prote, 2017; Ross et al., 1996; Lanoue et al., 2010). If these lesions are not properly repaired, they can eventually result in rearrangement of the mixed lineage leukemia (*MLL*) gene that makes HSPCs more vulnerable to further acquisition of secondary genetic changes following continued chemical-induced genotoxic insults *in utero* (https://aopwiki.org/aops/202) (Hernandez and Menendez, 2016; Greaves, 2015; Sanjuan-Pla et al., 2015; Pelkonen et al., 2017). By contrast, childhood leukemia may be the consequence of a two-hit model producing two independent (epi)genetic insults, the first one occurring *in utero* and the second one more often after birth (Cernaro et al., 2015; Kim et al., 2017; Perez-Perez et al., 2019). This difference in the biological initiating mechanisms of childhood and infant leukemia may explain the higher risk of infant leukemia related to pesticide exposure found in the present study. Specifically, in childhood leukemia, early *in utero* exposure to pesticides may result in oxidative stress, either directly by excessive generation of oxidative free radicals or indirectly by inhibition of antioxidant enzymes, leading to DNA single- and double-strand breaks in fetal HSPCs at specific cleavage sites (Carbone et al., 2018). If non-repaired or mis-repaired by non-homologous end-joining, these DNA lesions have the potential to form leukemia-causing chromosome rearrangements (duplications, deletions and translocations) (Deweese and Osheroff, 2009; Jan and Majeti, 2013). It is worth noting that the greater sensitivity of HSPCs to genotoxic insult during development can be due to a high content of topoisomerase II, a higher proliferation rate, and a lower ability of DNA repair of these cells (Panel on Plant Prote, 2017; Greaves and Wiemels, 2003; Swaminathan et al., 2015). Overall, a common initiating pathogenic event that represents a hallmark for both infant and childhood leukemia is the occurrence of chromosomal translocations that create fusion genes encoding chimeric fusion proteins (i.e., transcriptional factors) involved in the regulation of early hematopoiesis (Hernandez and Menendez, 2016; Bernat et al., 2018; Lerro et al., 2020).

Beyond these changes, recent studies have also focused on the effect of pesticide exposure on epigenetic reprogramming during critical windows of susceptibility, especially during pregnancy (Hernandez and Menendez, 2016; Chappell et al., 2016; Godschalk et al., 2020; Humphrey et al., 2019; Gorokhova et al., 2020). Emerging data provide evidence that persistent or repeated background exposure to pesticides during pregnancy may result in detrimental alterations to the epigenome and gene expression profile of stem cells, positioning these cells for malignant transformation and the development of childhood AL (Chappell et al., 2016; Dik et al., 2012). An example of such an exposure are the organochlorines (OC), a class of pesticides characterized by low water solubility, highly lipophilic nature and the capability of bioaccumulation (Rull et al., 2009a). Especially OC insecticides have been shown to induce epigenetic changes including disruption of DNA methylation and hypomethylation, changes to covalent histone alterations and associated chromatin remodeling, as well as non-coding RNA mediated regulation of gene expression (Humphrey et al., 2019; Shutoh et al., 2009; Wu et al., 2019). In the present study, the significant association between insecticide exposure during pregnancy and childhood AL might be mediated by the aforementioned pathogenic mechanisms. Future research is needed to confirm these epidemiologic findings, focusing specifically on the role of OC insecticides. Unfortunately, in our study only one study examining OC insecticides in relation to childhood AL was identified, which yielded statistically significant results (Ferreira et al., 2013); thus, a quantitative synthesis to summarize the evidence concerning OC insecticides was not feasible at this stage.

Although pesticides are regulated products subject to an extensive toxicological evaluation before being approved for use in agriculture, current regulatory guideline studies have potential limitations. In particular, the possible higher sensitivity of the HSPCs is not considered by the genotoxicity assays, and the usual treatment does not cover the early *in utero* development phase in the carcinogenicity assay (Panel on Plant Prote, 2017).

4.4. Critical appraisal: strengths and limitations

The present study acknowledges that the systematic review of environmental epidemiology, especially on pesticides, is a rather challenging field of research mainly due to the large heterogeneity of available evidence and several inherent limitations of the individual studies. The assessment of exposure is perhaps the most important methodological limitation of the studies. Despite the wide range of categories of pesticides studied, eligible studies mostly concentrated on a broadly defined pesticide category. Pesticides is a heterogeneous group of very different active chemical ingredients, even within their broad application group of insecticides, herbicides, fungicides, and others; few studies had information on specific pesticides and in the majority of studies, they were simply lumped together, mixing potentially chemicals of no effects to rather significant effects (Brouwer et al., 2016). Thus, in terms of risk characterization, the existing framework around risk assessment of pesticides, including both the lack of studies on compound-specific pesticides and the weaknesses in exposure assessment, has made it difficult to use epidemiological evidence when evaluating individual substances. Moreover, due to the large heterogeneity in exposure assessment, we aimed to separate by specific exposure groups, exposed populations and periods of exposure, which resulted in a small, by necessity, number of eligible studies included in each meta-analysis ($n \geq 2$). However, despite the lack of clarity in terms of exposure to specific substances and uncertainties on actual level of exposure, overall evidence suggests that there is a potential hazard. Though studies with more robust exposure assessment would be helpful,

the non-persistent nature of most pesticides and the use of multiple substances applied for crop protection makes it impossible to disentangle independent effects as can be done under laboratory conditions in animals. Such integrating existing evidence will not be fully solved by having better exposure data as co-exposures cannot be fully accounted for in observational setting. Some adaptation of existing risk assessment paradigms may also be needed.

Among other limitations, certain studies examined pesticides that have already been banned in western populations and the European Union. In addition, the measurement of biomarker levels as means of exposure assessment was available only in four studies. Owing to the rarity of childhood leukemia, cohort studies represented a minority of this literature with case-control studies accounting for the overwhelming majority of available evidence. Case-control evidence is prone to selection bias and is less robust to provide support to the causality of associations. There were few data regarding frequency or duration of pesticide exposure, with most studies based on self-reported exposure to pesticides, defined as "any versus never" use. However, such methods are prone to misclassification bias; especially in the case of retrospective studies, misclassification might be differential with higher exposures reported in participants with disease (recall bias). Schüz et al. investigated the potential impact of recall bias in the German case-control study, suggesting an inflation of the observed association was likely, but could not explain the positive association in its entirety (Schuz et al., 2003). Above all, self-reported exposure to pesticides based on questionnaires might allow the differentiation of subjects with very high and very low exposure levels, but it is not capable of valid exposure classification across an exposure gradient thus not allowing the study of dose-response relationships. Furthermore, the accuracy of exposure might be high for broad categories of pesticides and for commonly used pesticides, but not for specific pesticides. In addition, the statistical power of the Cochran's Q test for the assessment of heterogeneity was limited because of the small number of included studies. Concurrent exposure to multiple agents is also common, and it could thus introduce further bias in the results. For example, occupational exposure to pesticides might coexist with exposure to benzene, heavy metals, solvents, and suspended particulate matter, all of which have been associated with adverse health outcomes. It is essential to account for confounding from potential co-exposure to multiple agents in order to delineate unbiased associations, but this has not been possible in the overwhelming majority of evidence assessed herein. Lastly, the high possibility for selective reporting and multiple testing should be acknowledged when interpreting the results of the present meta-analysis. Indeed, the individual studies reported a very wide range of analyses yielding an enormous amount of multiple hypothesis testing without appropriate adjustment, and thus resulting in a high probability of high false positive rate; even when studies presented only one analysis, selective reporting is always a possibility.

Nonetheless, beyond these limitations, the present study systematically reviewed all available evidence and quantified the risk of childhood AL for exposure to any pesticide and for exposure to major pesticide subgroups. Substantiation and generalization of the results was achieved by including more than 160,000 participants from over 30 countries. To minimize between-study heterogeneity and given the potentially different impact of pesticide exposure on childhood AL, we performed stratified meta-analyses by window of exposure, exposed individual and type of exposure. Owing to the different immunophenotypes of childhood AL, we also performed separate analyses by major leukemia types (ALL and AML). In addition, we run subgroup meta-analyses by age group to explore the potentially different effect of pesticide exposure on the risk of infant leukemia, which constitutes a distinct leukemia entity (Schwaller, 2019). Unfortunately, only one study (Bailey et al., 2014) had information on ALL subtypes, namely B-cell and T-cell ALL; thus, further sub-analyses by ALL subtype were not feasible at this stage. Heterogeneity was minimal in most meta-analyses, whereas no publication bias was evident in the majority of analyses.

4.5. Conclusions

In the present systematic review and meta-analysis, we aimed to assess all types of pesticides in relation to childhood AL. However, our exhaustive search strategy showed that mostly unspecified pesticides or broad categories of pesticides have been studied to date. Evidence on specific classes of pesticides or biomonitoring data in biological samples is still limited and should be further addressed by future better-implemented studies. Beyond the inherent limitations and biases that may affect the summary effect estimates, the findings of the present meta-analysis provide some evidence that low-dose long-term exposure to pesticides, mainly during pregnancy, increases the risk of childhood AL, especially among infants, supporting the still harmful role of pesticides. Further evidence from sufficiently powered studies that can characterize exposure to individual substances using repeated biomarker analyses or combination of biomarker analyses and other exposure matrices is needed to confirm whether there is public health merit in reducing prenatal exposure to pesticides as concerns childhood leukemia. Moreover, mechanistic studies are deemed necessary to shed light into potentially relevant molecular pathways that underlie these associations, if replicated in future research.

Credit author statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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